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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/866,354	05/30/97	FOX G	A-401B

HM12/0329

U S PATENT OPERATIONS DRC
M S 10 1 B
AMGEN INC
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EXAMINER	
HAYES,R	
ART UNIT	**PAPER NUMBER**
1645	11

DATE MAILED: 03/29/99

Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/866354	Fox et al.
Examiner	**Group Art Unit**
Vaughn	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 12/18/98.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 13-14, 17-23, 28-31, 70-74 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 13-14, 17-23, 28, 30-31, 70-74 is/are rejected.

☒ Claim(s) 29 is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 10

☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other_____

Office Action Summary

DETAILED ACTION

Response to Amendment

1. The amendment filed 12/18/98 has been entered.

2. The objection of claims 18, 20, 22-23 & 26 under 37 CFR 1.75(c) as being in improper form because the claims should refer to other claims in the alternative only, is withdrawn due to the amendment or cancellation of these claims.

3. The objection of claims 53-58 & 60 because it does not comply with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence, versus Figure numbers, is withdrawn due to the cancellation of these claims.

4. The rejection of claims 13 & 53 under 35 U.S.C. 112, second paragraph, as being indefinite for being dependent on nonelected base claims is withdrawn due to the amendment or cancellation of the claim.

5. The rejection of claims 17 & 54 under 35 U.S.C. § 112, second paragraph, as being ambiguous is withdrawn due to the amendment or cancellation of the claim.

6. Claim 29 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. Applicant's arguments filed 12/18/98 have been fully considered but they are not deemed to be persuasive.

8. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. Claims 20-22 & new claim 52 are again rejected under 35 U.S.C. 101 because the claimed invention is still directed to non-statutory subject matter, for the reasons made of record, and as follows.

Similar to that previously made of record, a transformed or transfected host cell still encompasses a human organism subjected to gene therapy. It is again suggested that amending claim 21 to an "isolated" host cell should obviate this particular rejection.

10. Claims 13-14, 17-23, 28-31 & 70-74 are now provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-26, 28-31 & 51-54 of copending Application No. 08/837199 . Although the conflicting claims are

not identical, they are not patentably distinct from each other because the consensus sequences of SEQ ID NOs: 43 and 44 encompass that claimed in 08/837199, as does the hybridization language of claims 17 & 70.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 14, 17-18, 20, 22-23 & 70-74 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

No proper antecedent basis nor conception is apparent within the specification for the less stringent hybridization conditions of "4X SSC at 45-55^{0}C", or "[random] hybridization with 30-40% formamide..." or under "[undefined] stringent conditions" or "conditions of relaxed stringency"; thereby, constituting new matter (i.e., as it relates to claims 17 & 70).

No antecedent basis nor conception is apparent for "Cys^{40} through Cys^{421} of SEQ ID NO:36" within the specification (i.e., as it relates to clams 14(a)). In particular, page 19 of the specification conceptualizes only such analogs in which deletions of the amino terminus are made "without removing the first cysteine residue" (i.e., not removing Cys8); thereby, constituting new matter.

12. Claims 13-14, 17-23, 28, 30-31 & 70-74 are again rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific isolated human and rat nucleic acid molecules of SEQ ID NOs. 35, 37, 39 & 41, does not reasonably provide enablement for any nucleic acid sequence comprising a sequence that encodes any biologically functional equivalent GDNFR protein with little structural characteristics (e.g., SEQ ID NO: 43-44), or hybridization product thereof, with no known functional characteristics. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons made of record.

As previously made of record, the specification does not teach which particular amino acids are critical for any GDNF receptor protein's function that are encoded by these polynucleotides; nor how to distinguish any "analog thereof" (i.e., as it still relates to SEQ ID Nos: 43-44) or "hybridization" product of the instant invention from any other nucleic acid molecule that possesses none of the desired functions of the instant invention. Therefore, the skilled artisan would reasonably expect that any such random mutations to a nucleic acid encoding a putative GDNFR-related molecule would result in a polynucleotide encoding an inactive protein without requiring undue experimentation to discover how to make and use Applicants' invention; consistent with the teachings of Rudinger previously made of record. It is again suggested that amending the claims to recite a assayable function that is disclosed within an Example taught within the specification, which distinguishes the instant invention from different nucleic acid

molecules, should obviate this particular rejection (e.g., binding to GDNF and mediating a definable response to GDNF, versus any structurally undefined neurotrophic factor, or indefinite assay).

13. Claims 17-18, 20 & 22-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unknown, nor disclosed what metes and bounds of "stringent hybridization conditions" entail (i.e., as it relates to claim 17), in that it is unknown whether low, moderate or high stringent conditions are envisioned.

Additionally, claim 17(a) recites "encoding Met^{1} through Leu^{460} ..." when SEQ ID NO: 39 appears to encode 506 amino acid residues, versus 460 residues; thereby, being ambiguous. Further it is unclear at what specific nucleotide position Met^{1} is encoded, because none is recited, in which SEQ ID Nos: 35, 37, 39 & 41 are nucleotide sequences versus amino acid sequences.

14. Claim 22 is again rejected under 35 U.S.C. § 112, second paragraph, for lacking proper antecedent basis for "mammalian cells" and "bacterial cells" (i.e., as it relates to claim 22), versus the "host **cell**" recited in base claim 20.

15. Claim 28 is again rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: when a neurotrophic factor protein is to "complexed" by the receptor protein, as recited in the preamble.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

Priority is not granted from the filing date of the provisional applications because the provisional applications did not described the nucleotide/amino acid sequences of Figs. 14-17, 19 & 26 (i.e., did not conceptualize SEQ ID Nos: 35-44), including the consensus sequences, now claimed.

17. Claims 13-14, 17-23, 28, 30-31 & 70-74 are rejected under 35 U.S.C. 102(a) as being anticipated by Baloh et al. (IDS REF #CA)

Baloh et al. disclose a polynucleotide encoding a GDNF receptor-related protein which inherently hybridizes under stringent or reduced stringent conditions to SEQ ID Nos: 35, 37, 39

or 41 (e.g., at positions 710-2061 of SEQ ID NO:39; positions 203-1405 of SEQ ID NO:37; 1553-3077 of SEQ ID NO:35; positions 15-1372 of SEQ ID NO: 41), or hybridizes to a polynucleotide that encodes the amino acid sequences depicted in SEQ ID Nos: 36, 38, 40, 42, 43 or 44 (i.e., as it relates to claims 17 & 70), and further appears to comprise the consensus sequence depicted as SEQ ID Nos: 43 or 44 (i.e., as it relates to claims 13-14, 28 & 30; Fig. 1). In that this Baloh's polynucleotide sequence was cloned in the vector, pBluescript KS and pCMV-neo, transfected in *E.coli* and NIH3T3 mammalian fibroblasts, respectively, in which Baloh's TMR2-Ret protein is subsequently expressed and isolated from these fibroblasts, the limitations of claims 18-23, 28, 30-31 and 71-74 are met (pg. 800, 2nd col.).

18. Claims 13-14, 17-23, 28, 30-31 & 70-74 are rejected under 35 U.S.C. 102(a) as being anticipated by Jing et al. (IDS REF #CC). It is noted that the three inventors of the instant invention are different from the fourteen authors of this reference

Jing et al. disclose a polynucleotide encoding a GDNF receptor protein which inherently hybridizes under stringent or reduced stringent conditions to SEQ ID Nos: 35 or 39 (e.g., 100% identity at residues 1861-1888, 1908-1921, 2079-2096, 2234-2052, only one mismatch between residues 2168-2197, and only 8 mismatches between residues 1854-1921 of SEQ ID NO:35; 100% identity at residues 946-973, 1326-1342, only 2 mismatches between residues 1150-1181, and only 4 mismatches between residues 1719-1761 of SEQ ID NO:39), or hybridizes to a polynucleotide that encodes the amino acid sequences depicted in SEQ ID Nos: 36, 40, 43 or 44

(i.e., as it relates to claims 17& 70), and further appears to comprise the consensus sequence depicted as SEQ ID Nos: 43 or 44 (i.e., as it relates to claims 13-14, 28 & 30; Fig. 2). In that Jing's polynucleotide sequence was cloned in the vector, pBJ5 and pSJA45 and pDSRα2, transfected in *E.coli* and Neuro-2a cells and CHO cells, respectively, in which expression and isolation of Jing's GDNFR protein was obtained, the limitations of claims 18-23, 28, 30-31 and 71-74 are met (pg. 1121-1122).

19. Claims 13-14, 17-23, 28, 30-31 & 70-74 are rejected under 35 U.S.C. 102(a) as being anticipated by Treanor et al. (IDS REF #DJ).

Treanor et al. disclose a polynucleotide encoding a GDNF receptor-related protein which inherently hybridizes under stringent or reduced stringent conditions to a polynucleotide that encodes the amino acid sequences depicted in SEQ ID Nos: 36/35 (e.g., 100% identity between amino acid residue #s 57-63, 93-102, 195-209, 231-237, 264-271, 305-313 & 350-358), 43 or 44 (i.e., as it relates to claims 17 & 70), and further appears to comprise the consensus sequence depicted as SEQ ID Nos: 43 or 44 (i.e., as it relates to claims 13-14, 28 & 30; Fig. 1a). In that Treanor's polynucluceotide sequence was cloned in the *E.coli* and CHO expression vectors, in which Treanor's GDNFR protein was expressed, the limitations of claims 18-23, 28, 30-31 and 71-74 are met (pg. 81, Fig. 1).

20. Claims 13-14, 17-23 & 70-72 are rejected under 35 U.S.C. 102(a) as being anticipated by Wartiovaara et al.

Wartiovaara et al. disclose a GDNF receptor nucleotide and amino acid sequence that inherently hybridizes under stringent or reduced stringent conditions to SEQ ID Nos: 35 or 39 (e.g., 99.7% identical to SEQ ID NO:35 and 90.6% identical to SEQ ID NO:39; GenBank Accession Nos. 015316 and U93703, respectively, submitted March 6, 1997), or hybridizes to a polynucleotide that encodes the amino acid sequences depicted in SEQ ID Nos: 36, 40, 43 or 44 (e.g. 99.1% identical to SEQ ID NO:36, 94% identical to SEQ ID NO:40; as it relates to claims 17& 70), and further appears to comprise the consensus sequence depicted as SEQ ID Nos: 43 or 44 (i.e., as it relates to claims 13-14, 28 & 30). In that Wartiovaara's sequences are contained in a sequencing vector transformed into *E.coli,* in order to obtain the disclosed sequences, the limitations of claims 18-23 and 71-72 are anticipated.

According to information provided by GenBank user services, sequences submitted to GenBank are processed and immediately placed into the public database unless the author(s) have requested that the sequences be withheld pending publication of an article. Processing typically takes from 2-3 days to a period of weeks. Sequences submitted to EMBL or DDBJ are transmitted to GenBank within 24 hours of their receipt. It therefore reasonably appears, absent evidence to the contrary, that the cited GenBank record was available to the public shortly after its submission date and constitutes prior art under 35 U.S.C. § 102 (a).

It is noted that this rejection is based in part upon a disclosure provided in a computer database record. Because the database was indexed so as to be available to the relevant part of the public, it is considered to be a U.S.C. § 102; see *In re Wyer*, 210 USPQ 790.

21. Claims 13-14, 17-23 & 70-72 are rejected under 35 U.S.C. 102(a) as being anticipated by Watabe.

Watabe discloses a GDNF receptor nucleotide and amino acid sequence that inherently hybridizes under stringent or reduced stringent conditions to SEQ ID Nos: 35 or 39 (e.g., 100% identical to residue #s 1865-1888, 2168-2191, 2241-2259, and only two mismatches between residues 2079-2114 of SEQ ID NO:35; and 100% identical to residue #s 946-973, 1253-1276, and only four mismatches between residues 1150-1199, etc. of SEQ ID NO:39; GenBank Accession Nos. AB000800, submitted January 30, 1997), or hybridizes to a polynucleotide that encodes the amino acid sequences depicted in SEQ ID Nos: 36, 40, 43 or 44 (i.e., as it relates to claims 17& 70), and further appears to comprise the consensus sequence depicted as SEQ ID Nos: 43 or 44 (i.e., as it relates to claims 13-14, 28 & 30) In that Watabe's sequences are contained in a sequencing vector transformed into *E.coli,* in order to obtain the instant sequences, the limitations of claims 18-23 and 71-72 are anticipated.

According to information provided by GenBank user services, sequences submitted to GenBank are processed and immediately placed into the public database unless the author(s) have requested that the sequences be withheld pending publication of an article. Processing typically

takes from 2-3 days to a period of weeks. Sequences submitted to EMBL or DDBJ are transmitted to GenBank within 24 hours of their receipt. It therefore reasonably appears, absent evidence to the contrary, that the cited GenBank record was available to the public shortly after its submission date and constitutes prior art under 35 U.S.C. § 102 (a).

It is noted that this rejection is based in part upon a disclosure provided in a computer database record. Because the database was indexed so as to be available to the relevant part of the public, it is considered to be a U.S.C. § 102; see *In re Wyer*, 210 USPQ 790.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
March 15, 1999

PATRICIA A. DUFFY
PRIMARY EXAMINER